EFSA NDA Panel (EFSA Panel on Dietetic Products, Nut rition and Allergies) , 2013. Scientific Opinion on the substantiation of a health claim related to the c onsum ption of 2 g/day of plant stanols (as plant stanol ester s) as part of a diet low in saturated fat and a two - fold greater reduction in blood LDL - chol esterol concentrations compared to the consumption of a diet low in saturated fat alone pursuant to Article 14 of Regulation (EC) No 1924/2006

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SCIENTIFIC OPINION

Scientific Opinion on the substantiation of a health claim related to the consumption of 2 g/day of plant stanols (as plant stanol esters) as part of a diet low in saturated fat and a two-fold greater reduction in blood LDL-cholesterol concentrations compared to the consumption of a diet low in saturated fat alone pursuant to Article 14 of Regulation (EC) No 1924/2006[1]

EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA)[2, 3]

European Food Safety Authority (EFSA), Parma, Italy

ABSTRACT

Following an application from McNeil Nutritionals and Raisio Nutrition Ltd, submitted for authorisation of a health claim pursuant to Article 14 of Regulation (EC) No 1924/2006 via the Competent Authority of the United Kingdom, the Panel on Dietetic Products, Nutrition and Allergies (NDA) was asked to deliver an opinion on the scientific substantiation of a health claim related to the consumption of 2 g/day of plant stanols (as plant stanol esters) as part of a diet low in saturated fat and a two-fold greater reduction in blood LDL-cholesterol concentrations compared to the consumption of a diet low in saturated fat alone. The food that is the subject of the health claim, plant stanol esters, is sufficiently characterised. The applicant provided five human intervention studies for the scientific substantiation of the claim. The Panel notes that the design of the studies submitted did not allow an evaluation of the quantitative effects of diets low in saturated fat *per se* on blood LDL-cholesterol concentrations. Therefore, the effect of consuming 2 g/day plant stanols as part of a diet low in saturated fat relative to the effect of consuming a diet low in saturated fat alone cannot be determined on a quantitative basis. The Panel considers that the evidence provided by the applicant does not establish that the consumption of 2 g/day of plant stanols (as plant stanol esters) as part of a diet low in saturated fat results in a two-fold greater reduction in LDL-cholesterol concentrations compared with consuming a diet low in saturated fat alone. A claim on plant stanol esters and reduction of blood LDL-cholesterol concentrations (irrespective of the background diet) has already been authorised in the European Union. © European Food Safety Authority, 2013

[1] On request from the Competent Authority of the United Kingdom following an application by McNeil Nutritionals and Raisio Nutrition Ltd, Question No EFSA-Q-2012-00915, adopted on 21 March 2013.

[2] Panel members: Carlo Agostoni, Roberto Berni Canani, Susan Fairweather-Tait, Marina Heinonen, Hannu Korhonen, Sébastien La Vieille, Rosangela Marchelli, Ambroise Martin, Androniki Naska, Monika Neuhäuser-Berthold, Grażyna Nowicka, Yolanda Sanz, Alfonso Siani, Anders Sjödin, Martin Stern, Sean (J.J.) Strain, Inge Tetens, Daniel Tomé, Dominique Turck and Hans Verhagen. Two members of the Panel did not participate in the discussion on the subject referred to above because of potential conflicts of interest identified in accordance with the EFSA policy on declarations of interests. Correspondence: nda@efsa.europa.eu

[3] Acknowledgement: The Panel wishes to thank the members of the Working Group on Claims: Carlo Agostoni, Jean-Louis Bresson, Susan Fairweather-Tait, Marina Heinonen, Ambroise Martin, Hildegard Przyrembel, Yolanda Sanz, Alfonso Siani, Anders Sjödin, Sean (J.J.) Strain, Inge Tetens, Hendrik Van Loveren, Hans Verhagen and Peter Willatts for the preparatory work on this scientific opinion.

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KEY WORDS

plant stanols, plant stanol esters, LDL-cholesterol, saturated fat, diet, health claims

SUMMARY

Following an application from McNeil Nutritionals and Raisio Nutrition Ltd, submitted for authorisation of a health claim pursuant to Article 14 of Regulation (EC) No 1924/2006 via the Competent Authority of the United Kingdom, the Panel on Dietetic Products, Nutrition and Allergies (NDA) was asked to deliver an opinion on the scientific substantiation of a health claim related to the consumption of 2 g/day of plant stanols (as plant stanol esters) as part of a diet low in saturated fat and a two-fold greater reduction in blood LDL-cholesterol concentrations compared to the consumption of a diet low in saturated fat alone.

The scope of the application was proposed to fall under a health claim referring to disease risk reduction.

The food that is the subject of the health claim is plant stanol esters. The Panel considers that plant stanol esters are sufficiently characterised.

The claimed effect is "consuming 2 g/day of plant stanols (as plant stanol esters) as part of a diet low in saturated fat results in a 2-fold greater reduction in LDL-cholesterol than consuming a low saturated fat diet alone; high cholesterol is a risk factor in the development of coronary heart disease". The target population proposed by the applicant is "adults with raised LDL-cholesterol levels who need and want to lower their blood cholesterol".

The Panel considers that reduction of blood LDL-cholesterol concentrations is a beneficial physiological effect. A reduction in blood LDL-cholesterol concentrations reduces the risk of coronary hear disease.

The present application refers to a claim on the consumption of 2 g/day of plant stanols (as plant stanol esters) as part of a diet low in saturated fat and a two-fold greater reduction in blood LDL-cholesterol concentrations compared to the consumption of a diet low in saturated fat alone. A diet low in saturated fat has been defined by the applicant as a diet containing less than or equal to 10 % of the total energy (E%) as saturated fat.

A claim on plant stanol esters and reduction of blood LDL-cholesterol concentrations has already been authorised in the European Union. The conditions of use for the claim (the beneficial effect is obtained with a daily intake of at least 1.5 g plant stanols) do not specify the background diet in the context of which plant stanol esters should be consumed in order to achieve the claimed effect and thereby imply that the claimed effect could be achieved irrespective of the background diet in which plant stanol esters are consumed.

The applicant performed a literature search up to November 2011 for randomised controlled trials in adults assessing blood LDL-cholesterol concentrations and using doses of plant stanols (as plant stanol esters) of 1.5 to 2.4 g/day in conjunction with a diet low in saturated fat (≤10 E%) with a duration of more than two weeks.

Through this literature search the applicant retrieved five human intervention studies. These studies were generally designed to investigate the effects of plant stanols, of plant sterols and stanols, or of different sources of plant stanols (wood and vegetable oil) on blood LDL-cholesterol concentrations in the context of diets low in saturated fat lasting between 3 and 16 weeks.

All of the studies provided included three intervention arms/periods. In three studies, the effect of consumption of plant stanols or plant sterols in the context of a low saturated fat diet were compared with the consumption of a low saturated fat diet plus placebo. In another study, two arms consumed plant stanols, either with the usual diet or with a diet low in saturated fat, and one arm received placebo plus the same diet low in saturated fat. In the fifth study, one arm received plant stanols plus a

diet low in saturated fat, one arm received placebo and the same diet low in saturated fat, and a third arm followed a "Mediterranean diet", the characteristics and composition of which were not specified.

The Panel notes that these studies were uncontrolled with respect to the effect of a low saturated fat diet without plant stanols on blood LDL-cholesterol concentrations owing to the lack of a reference diet without plant stanols in these studies, and that changes in blood LDL-cholesterol concentrations from baseline in the study arms consuming a low saturated fat diet plus placebo cannot be used to quantify the effects of diets low in saturated fat *per se* on blood LDL-cholesterol concentrations. The Panel therefore notes that the effect of consuming 2 g/day plant stanols as part of a diet low in saturated fat relative to the effect of consuming a diet low in saturated fat alone cannot be determined on a quantitative basis.

The Panel considers that the evidence provided by the applicant does not establish that the consumption of 2 g/day of plant stanols (as plant stanol esters) as part of a diet low in saturated fat results in a two-fold greater reduction in LDL-cholesterol concentrations compared with consuming a diet low in saturated fat alone.

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BACKGROUND

Regulation (EC) No 1924/2006[4] harmonises the provisions that relate to nutrition and health claims, and establishes rules governing the Community authorisation of health claims made on foods. As a rule, health claims are prohibited unless they comply with the general and specific requirements of this Regulation, are authorised in accordance with this Regulation, and are included in the lists of authorised claims provided for in Articles 13 and 14 thereof. In particular, Articles 14 to 17 of this Regulation lay down provisions for the authorisation and subsequent inclusion of reduction of disease risk claims and claims referring to children's development and health in a Community list of permitted claims.

According to Article 15 of this Regulation, an application for authorisation shall be submitted by the applicant to the national competent authority of a Member State, which will make the application and any supplementary information supplied by the applicant available to the European Food Safety Authority (EFSA).

STEPS TAKEN BY EFSA

- The application was received on 23/10/2012.
- The scope of the application was proposed to fall under a health claim referring to disease risk reduction.
- On 04/12/2012, during the validation process of the application, EFSA sent a request to the applicant to provide missing information.
- On 10/01/2013, EFSA received the missing information as submitted by the applicant.
- The scientific evaluation procedure started on 14/01/2013.
- On 24/01/2013, the NDA Panel agreed on a list of questions for the applicant to provide additional information to accompany the application. The clock was stopped on 28/01/2013 and restarted on 14/03/2013, in compliance with Article 16(1) of Regulation (EC) No 1924/2006.
- On 14/03/2013, EFSA received the requested information (which was made available to EFSA in electronic format on 07/03/2013).
- During its meeting on 21/03/2013, the NDA Panel, having evaluated the data submitted, adopted an opinion on the scientific substantiation of a health claim related to the consumption of 2 g/day of plant stanols (as plant stanol esters) as part of a diet low in saturated fat and a two-fold greater reduction in blood LDL-cholesterol concentrations compared to the consumption of a diet low in saturated fat alone.

TERMS OF REFERENCE

EFSA is requested to evaluate the scientific data submitted by the applicant in accordance with Article 16 of Regulation (EC) No 1924/2006. On the basis of that evaluation, EFSA will issue an opinion on the scientific substantiation of a health claim related to: the consumption of 2 g/day of plant stanols (as plant stanol esters) as part of a diet low in saturated fat and a two-fold greater reduction in blood LDL-cholesterol concentrations compared to the consumption of a diet low in saturated fat alone.

[4] Regulation (EC) No 1924/2006 of the European Parliament and of the Council of 20 December 2006 on nutrition and health claims made on foods. OJ L 404, 30.12.2006, p. 9–25.

EFSA DISCLAIMER

The present opinion does not constitute, and cannot be construed as, an authorisation for the marketing of plant stanol esters, a positive assessment of its safety, nor a decision on whether plant stanol esters are, or are not, classified as a foodstuff. It should be noted that such an assessment is not foreseen in the framework of Regulation (EC) No 1924/2006.

It should also be highlighted that the scope, the proposed wording of the claim, and the conditions of use as proposed by the applicant may be subject to changes, pending the outcome of the authorisation procedure foreseen in Article 17 of Regulation (EC) No 1924/2006.

INFORMATION PROVIDED BY THE APPLICANT

Applicant's name and address: McNeil Nutritionals, a division of Cilag GmbH International, 1 Landis & Gyr Strasse, 6300 Zug, Switzerland; Raisio Nutrition Ltd P.O. Box 101 (Raisionkaari 55), FI21201 Raisio, Finland.

Food/constituent as stated by the applicant

According to the applicant, the food constituent which is the subject of the claim is plant stanol esters consumed as part of a diet low in saturated fat (saturated fat intake ≤10 % of the total daily energy intake).

Health relationship as claimed by the applicant

According to the applicant, consuming 2 g/day plant stanols (as plant stanol esters) as part of a diet low in saturated fat results in a 2-fold greater reduction in LDL-cholesterol than consuming a low saturated fat diet alone. Reducing LDL-cholesterol reduces the risk of coronary heart disease.

Wording of the health claim as proposed by the applicant

The applicant has proposed the following wording for the health claim: "Consuming 2 g/day of plant stanols (as plant stanol esters) as part of a diet low in saturated fat results in a 2-fold greater reduction in LDL-cholesterol than consuming a low saturated fat diet alone. High cholesterol is a risk factor in the development of coronary heart disease."

Specific conditions of use as proposed by the applicant

According to the applicant, the target population includes male and female adults with raised LDL-cholesterol levels who need and want to lower their blood cholesterol. The applicant proposed an intake of 2 g of plant stanols (as plant stanol esters) that must be consumed daily as part of diet low in saturated fat in order to achieve the double the LDL-cholesterol-lowering effect.

ASSESSMENT

1. Characterisation of the food/constituent

The food that is the subject of the health claim is plant stanol esters.

Plant stanols occur naturally in free and esterified form in only small amounts in the daily diet. They can be industrially produced from vegetable oil sterols (vegetable sterols) and from tall oil sterols (wood sterols). Plant stanols are produced from the hydrogenation of plant sterols (e.g. sitosterol and campesterol) to plant stanols (e.g. sitostanol and campestanol). Plant stanol esters are the products derived from the esterification of plant stanols with fatty acids. The main plant stanols in a plant stanol blend are sitostanol and campestanol. Plant stanols produced from tall oil sterols, sourced in Scandinavia, contain approximately 94 % sitostanol and approximately 6 % campestanol. A blend of plant stanols obtained from typical commercial soybean oil based plant sterols contains 68–75 % sitostanol and 25–32 % campestanol. The fatty acids used for the esterification of the plant stanols are derived from vegetable oils or blends thereof.

Information pertaining to the manufacturing process, the batch-to-batch variability and stability has been provided by the applicant. Plant stanol esters can be analysed in foods by established methods.

The Panel considers that the food, plant stanol esters, which is the subject of the health claim, is sufficiently characterised.

2. Relevance of the claimed effect to human health

The claimed effect is "consuming 2 g/day of plant stanols (as plant stanol esters) as part of a diet low in saturated fat results in a 2-fold greater reduction in LDL-cholesterol than consuming a low saturated fat diet alone; high cholesterol is a risk factor in the development of coronary heart disease". The target population proposed by the applicant is "adults with raised LDL-cholesterol levels who need and want to lower their blood cholesterol".

Coronary heart disease (CHD) is a leading cause of mortality and morbidity in European populations with over 1.9 million deaths in the European Union and over 4.35 million deaths in Europe each year (Petersen et al., 2005). Elevated blood cholesterol is an important modifiable risk factor in the development of CHD (WHO, 2002).

It has been shown that blood cholesterol can be decreased by drugs, and by dietary and lifestyle changes (Ornish et al., 1998; Gordon, 2000; Law, 2000; Katan et al., 2003; Denke, 2005; Pedersen et al., 2005; Van Horn et al., 2008).

The present application refers to a claim on the consumption of 2 g/day of plant stanols (as plant stanol esters) as part of a diet low in saturated fat and a two-fold greater reduction in blood LDL-cholesterol concentrations compared to the consumption of a diet low in saturated fat alone. A diet low in saturated fat has been defined by the applicant as a diet containing less than or equal to 10 % of the total energy (E%) as saturated fat.

The Panel considers that reduction of blood LDL-cholesterol concentrations is a beneficial physiological effect. A reduction in blood LDL-cholesterol concentrations reduces the risk of CHD.

3. Scientific substantiation of the claimed effect

A claim on plant stanol esters and reduction of blood LDL-cholesterol concentrations has already been authorised in the European Union[5]. The conditions of use for the claim (the beneficial effect is obtained with a daily intake of at least 1.5 g plant stanols) do not specify the background diet in the context of which plant stanol esters should be consumed in order to achieve the claimed effect and thereby imply that the claimed effect could be achieved irrespective of the background diet in which plant stanol esters are consumed. Indeed, the scientific substantiation of the claim on plant stanol esters and reduction of blood LDL-cholesterol concentrations was primarily based on a number of human intervention studies showing a significant effect of plant stanol esters on blood LDL-cholesterol concentrations compared to placebo. Such studies differed with respect to the fat composition and fat content of the background diet, and included four out of the five human intervention studies which have been submitted by the applicant for the scientific substantiation of the current claim.

The applicant performed a literature search in Medline, Allied & Complementary Medicine, Foodline: Science, CAB Abstracts, Elsevier Biobase, National Technical Information Service, EMBASE and Adis Clinical Trails Insight up to November 2011 for randomised controlled trials in adults assessing blood LDL-cholesterol concentrations and using doses of plant stanols (as plant stanol esters) of 1.5 to 2.4 g/day in conjunction with a diet low in saturated fat (≤10 E%) with a duration of more than two weeks. Studies published as abstracts or not published in a peer-reviewed journal or in which free

[5] Commission Regulation (EC) No 983/2009 of 21 October 2009 on the authorisation and refusal of authorisation of certain health claims made on food and referring to the reduction of disease risk and to children's development and health. OJ L 277, 22.10.2009, p. 3–12.

plant stanols, or plant sterols or a blend of plant stanols and sterols were administered, or where the dose of plant stanols (as plant stanol esters) was not specified or was outside the pre-specified range or where the background diet did not consist of a diet low in saturated fat were excluded. Keyword used to retrieve publications included: [plant()sterol? or plant()stanol? or phytosterol? or phytostanol? or sitosterol? or sitostanol? or campesterol? or campestanol? or stigmasterol? or brassicasterol?] AND [LDL()cholesterol? or low()density()lipoprotein()cholesterol? or cholesterol? or lipid?].

Through this literature search the applicant retrieved five human intervention studies (Andersson et al., 1999; Hallikainen and Uusitupa, 1999; Hallikainen et al., 2000; Jones et al., 2000; Athyros et al., 2011).

These studies were generally designed to investigate the effects of plant stanols (Andersson et al., 1999; Athyros et al., 2011), of plant sterols and stanols (Hallikainen et al., 2000; Jones et al., 2000), or of different sources of plant stanols (wood and vegetable oil) (Hallikainen and Uusitupa, 1999) on blood LDL-cholesterol concentrations in the context of diets low in saturated fat lasting between 3 and 16 weeks. Two studies were of cross-over design (Hallikainen et al., 2000; Jones et al., 2000) while the remaining studies had a parallel design.

All of the studies provided included three intervention arms/periods. In three studies (Hallikainen and Uusitupa, 1999; Hallikainen et al., 2000; Jones et al., 2000), the effect of consumption of plant stanols or plant sterols in the context of a low saturated fat diet were compared with the consumption of a low saturated fat diet plus placebo. In another study (Andersson et al., 1999), two arms consumed plant stanols, either with the usual diet or with a diet low in saturated fat, and one arm received placebo plus the same diet low in saturated fat. In the fifth study (Athyros et al., 2011), one arm received plant stanols plus a diet low in saturated fat, one arm received placebo and the same diet low in saturated fat, and a third arm followed a "Mediterranean diet", the characteristics and composition of which were not specified in the publication. Upon a request from EFSA to provide information on the composition of the "Mediterranean diet", the applicant indicated that this study arm was not appropriately blinded and was therefore not considered relevant by the applicant, and did not provide any compositional information.

The Panel notes that these studies were uncontrolled with respect to the effect of a low saturated fat diet without plant stanols on blood LDL-cholesterol concentrations owing to the lack to of a reference diet without plant stanols in these studies, and that changes in blood LDL-cholesterol concentrations from baseline in the study arms consuming a low saturated fat diet plus placebo cannot be used to quantify the effects of diets low in saturated fat *per se* on blood LDL-cholesterol concentrations. The Panel therefore notes that the effect of consuming 2 g/day plant stanols as part of a diet low in saturated fat relative to the effect of consuming a diet low in saturated fat alone cannot be determined on a quantitative basis.

The Panel considers that the evidence provided by the applicant does not establish that the consumption of 2 g/day of plant stanols (as plant stanol esters) as part of a diet low in saturated fat results in a two-fold greater reduction in LDL-cholesterol concentrations compared with consuming a diet low in saturated fat alone.

A claim on plant stanol esters and reduction of blood LDL-cholesterol concentrations (irrespective of the background diet) has already been authorised in the European Union.

CONCLUSIONS

On the basis of the data presented, the Panel concludes that:

- The food constituent, plant stanol esters, which is the subject of the health claim, is sufficiently characterised.

- The claimed effect proposed by the applicant is "consuming 2 g/day of plant stanols (as plant stanol esters) as part of a diet low in saturated fat results in a 2-fold greater reduction in LDL-cholesterol than consuming a low saturated fat diet alone; high cholesterol is a risk factor in the development of coronary heart disease." The target population proposed by the applicant is "adults with raised LDL-cholesterol levels who need and want to lower their blood cholesterol".

- The evidence provided by the applicant does not establish that the consumption of 2 g/day plant stanols (as plant stanol esters) as part of a diet low in saturated fat results in a two-fold greater reduction in LDL-cholesterol concentrations compared with consuming a diet low in saturated fat alone.

DOCUMENTATION PROVIDED TO EFSA

Application for a health claim related the consumption of 2 g/day of plant stanols (as plant stanol esters) as part of a diet low in saturated fat and a two-fold greater reduction in blood LDL-cholesterol concentrations compared to the consumption of a diet low in saturated fat alone (Claim serial No: 0368_UK). January 2013. Submitted by McNeil Nutritionals and Raisio Nutrition Ltd.

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GLOSSARY AND ABBREVIATIONS

CHD Coronary heart disease

LDL Low-density lipoprotein